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# Modelling of Glucose-Insulin-Glucagon Pharmacodynamics in Man

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**Abstract**—The purpose is to build a simulation model of the glucoregulatory system in man. We estimate individual human parameters of a physiological glucose-insulin-glucagon model. We report posterior probability distributions and correlations of model parameters.

## I. INTRODUCTION

In healthy individuals, insulin and glucagon work in a complex fashion to maintain blood glucose levels within a narrow range. Recent studies suggest a multiplicative effect of insulin and of glucagon on endogenous glucose production (EGP) [1].

## II. MATERIALS AND METHODS

### A. PD Model

The pharmacodynamics (PD) model is mainly inspired by Hovorka et al. [2].

$$\dot{Q}_1(t) = -F_{01} - S_T x_1(t) Q_1(t) + k_{12} Q_2(t) + F_{IC}(t) \quad (1a)$$

$$\dot{Q}_2(t) = S_T x_1(t) Q_1(t) - (k_{12} + S_D x_2(t)) Q_2(t) \quad (1b)$$

$$\dot{x}_i(t) = k_i (I(t) - x_i(t)) \quad i = 1, 2, 3 \quad (1c)$$

$Q_1(t)$  and  $Q_2(t)$  are the masses of glucose per bodyweight ( $\mu\text{mol/kg}$ ) in the accessible and non-accessible compartments. Glucose concentration ( $\text{mmol/L}$ ) in the accessible compartment is  $Q_1(t)/V$  with  $V$  fixed at  $160 \text{ mL/kg}$ .  $I(t)$  is the insulin concentration ( $\text{mIU/L}$ ) in the accessible compartment.  $x_i(t)$  are the remote effects of insulin ( $\text{mIU/L}$ ).

$F_{01}$  is the non-insulin-dependent glucose flux.  $k_{12}$  and  $k_i$  are transfer rate constants.  $S_D$ ,  $S_E$ , and  $S_T$  are insulin sensitivities.

The model in (1) is modified so  $F_{IC}(t)$  is the insulin and glucagon dependent EGP [3].

$$F_{IC}(t) = \frac{(1 - S_E x_3(t))}{(1 - S_E I_{b,y})} \cdot \left( (E_{max} - E_0) \frac{C(t)}{C_{E50} + C(t)} \right) \quad (2)$$

$C(t)$  is the glucagon concentration ( $\text{pg/mL}$ ) in the accessible compartment.  $I_{b,y}$  is the fixed basal insulin concentration ( $\text{mIU/L}$ ) for subject  $y$ , and  $E_0$  is the minimum EGP fixed at  $8 \mu\text{mol/(kg}\cdot\text{min)}$ .  $E_{max}$  is the maximum EGP at  $I_{b,y}$ .  $C_{E50}$  is the glucagon concentration at half maximum EGP.

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### B. Parameter Estimation

We used maximum a posteriori to estimate PD model parameters and profile likelihood analysis to reduce unidentifiable parameters in data with measurements of glucose, insulin and glucagon from ten healthy male subjects who received a  $1 \text{ mg}$  subcutaneous bolus of marketed glucagon.

## III. RESULTS

TABLE I

POSTERIOR DISTRIBUTIONS OF PARAMETERS ACROSS POPULATION.

Parameter	Unit	Mean	SD
$C_{E50}$	$\text{pg/mL}$	407	39
$E_{max}$	$\mu\text{mol/(kg}\cdot\text{min)}$	38.8	5.0
$F_{01}$	$\mu\text{mol/(kg}\cdot\text{min)}$	10.5	0.95
$\ln(k_{12})$	$\text{min}^{-1}$	-3.48	0.26
$\ln(k_2)$	$\text{min}^{-1}$	-2.11	0.03
$\ln(k_3)$	$\text{min}^{-1}$	-4.20	0.74
$\ln(S_E)$	per $\text{mIU/L}$	-3.19	0.67
$\ln(S_T)$	$\text{min}^{-1}$ per $\text{mIU/L}$	-5.73	0.54
$\ln(k_1)$	$\text{min}^{-1}$	-5.69	*
$\ln(S_D)$	$\text{min}^{-1}$ per $\text{mIU/L}$	-7.58	*

\* Fixed unidentifiable parameter.

TABLE II

POSTERIOR CORRELATION MATRIX OF IDENTIFIABLE PARAMETERS.

	$C_{E50}$	$E_{max}$	$F_{01}$	$k_{12}^*$	$k_2^*$	$k_3^*$	$S_E^*$	$S_T^*$	BW
$C_{E50}$	1								
$E_{max}$	0.31	1							
$F_{01}$	0.32	-0.30	1						
$k_{12}^*$	0.45	0.23	0.22	1					
$k_2^*$	-0.63	0.06	-0.13	-0.30	1				
$k_3^*$	0.13	-0.34	0.82	-0.02	-0.33	1			
$S_E^*$	-0.82	-0.26	-0.40	-0.22	0.43	-0.35	1		
$S_T^*$	-0.20	-0.22	-0.13	0.45	-0.28	-0.14	0.57	1	
BW	0.61	-0.43	0.39	0.24	-0.70	0.42	-0.60	0.00	1

\* Correlation of  $\ln$ -transformed parameter.

## IV. CONCLUSIONS

The model enables simulations of the glucose-insulin-glucagon dynamics in man at the following concentrations: glucagon ( $180\text{--}8000 \text{ pg/mL}$ ), insulin ( $1.2\text{--}81.9 \text{ mIU/L}$ ) and glucose ( $3.3\text{--}11.5 \text{ mmol/L}$ ).

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